Posaconazole (Noxafil): a new triazole antifungal agent

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Posaconazole is the newest triazole antifungal agent. It is structurally related to itraconazole and has activity against *Candida* species, *Aspergillus* species, *Cryptococcus neoformans,* the zygomycetes, and other filamentous fungi. Randomized, double-blind trials have shown posaconazole to be at least as efficacious as fluconazole for the prevention of invasive fungal infections in immunocompromised patients. It has also shown promising results in the treatment of various fungal infections refractory to other antifungal therapy. The dose of posaconazole is 200 mg orally three times daily for the prevention of invasive fungal infections and 800 mg daily in two to four divided doses for the treatment of invasive fungal infections refractory to other antifungal treatment. All posaconazole doses should be given with food or a nutritional supplement to enhance absorption. The most common adverse effects reported with posaconazole therapy were fever, diarrhea, nausea, vomiting, and headache. Instances of elevated liver enzyme levels, hyperbilirubinemia, and hepatocellular damage were also noted in clinical trials, and these laboratory values should be monitored during treatment with posaconazole.

Fungal infections remain an important cause of morbidity and mortality in hospitalized patients (1). Patients who are immunocompromised are at highest risk of developing fungal infections, although severely ill patients in the intensive care unit are also at risk (2). Infections caused by *Candida* species are now more commonly seen in patients in the intensive care unit than in those who are immunocompromised. An increase in the incidence of infections caused by non-*albicans Candida* species has been noted in recent years. Immunocompromised patients are also at high risk of developing mold infections. The most common mold infections are caused by *Aspergillus* species, although an increase in mold infections due to *Scedosporium* species, *Fusarium* species, and zygomycetes has been noted.

The current antifungal armamentarium includes amphotericin B (AmB) formulations, echinocandins, flucytosine, and triazole antifungals. AmB has a broad spectrum of activity and is recommended as first-line therapy for many fungal infections; however, its use is limited by the high incidence of toxicity. Lipid formulations of AmB have efficacy similar to that of AmB but a lower incidence of toxicity. For this reason, lipid formulations of AmB are often used first when AmB treatment is needed despite their higher cost. Echinocandins have broad spectrums of activity and few adverse events associated with their use. They are commonly used as first-line agents for infections caused by *Candida* species. However, they lack oral formulations and have no activity against zygomycetes or the endemic mycoses, including *Cryptococcus*. Flucytosine is generally used in combination with other antifungals due to the rapid development of resistance to this agent when used alone. Triazole antifungals include fluconazole, itraconazole, voriconazole, and the newest agent, posaconazole. Fluconazole and voriconazole are both available as intravenous and oral formulations and have favorable safety profiles. Itraconazole is active against *Aspergillus* species and resistant strains of *Candida* species, but absorption with the oral formulations is a problem.

Posaconazole (Noxafil, Schering Corporation, Kenilworth, NJ) was approved by the Food and Drug Administration for use as prophylaxis against invasive *Aspergillus* and *Candida* infections in immunocompromised patients. This group includes patients undergoing hematopoietic stem cell transplantation who have graft-versus-host disease and patients with hematological malignancies who are receiving chemotherapy (3). This triazole antifungal agent, which is structurally similar to itraconazole (4, 5), has a broad spectrum of activity and has coverage against emerging fungi such as the zygomycetes. Studies have shown it to be a promising agent for the treatment of fungal infections as well.

PHARMACOLOGY

Like the other triazole antifungals, posaconazole inhibits the fungal enzyme lanosterol 14-alpha-demethylase (3–5). A reduction in this enzyme causes a decrease in fungal ergosterol synthesis, which is vital for the formation of fungal cell walls.

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Table 1. Pharmacokinetic properties of triazole antifungals*

Property	Posaconazole	Voriconazole	Fluconazole	Itraconazole
Bioavailability	Variable	>95%	>90%	50%–75%
Protein binding	>90%	58%	11%	99%
Volume of distribution	1774 L	4.6 L/kg	0.7–0.8 L/kg	11 L/kg
Time to maximum concentration	4–5 hours	1–2 hours	2–4 hours	4–5 hours
Metabolism	Hepatic: glucuronidation to inactive metabolites	Hepatic: CYP2C19, 2C9, 3A4	Hepatic: 11% metabolized	Hepatic: CYP3A4
Elimination half-life	25–35 hours	6–24 hours (variable)	22–31 hours	35–64 hours
Elimination route	<1% excreted unchanged in urine; 66% excreted unchanged in feces	Hepatic; <2% excreted unchanged in urine	80% excreted unchanged in urine	Hepatic; <1% excreted unchanged in urine

*From references 3–8.

The cell wall abnormalities result in either cell death or blunted cell growth.

PHARMACOKINETICS

Table 1 summarizes the pharmacokinetic properties of posaconazole and the other triazole antifungals (3–8).

Courtney and colleagues conducted a randomized, open-label, crossover, single-dose study in 20 adult men to evaluate the effect of food on the bioavailability of two formulations of posaconazole (9). Subjects were given posaconazole 200 mg as suspension with a high-fat breakfast, as suspension with a nonfat breakfast, or as tablets with a high-fat breakfast after a 10-hour fast. Drug exposure was greater, as shown by an increase in the area under the curve (AUC) of 37%, when posaconazole was given in suspension rather than tablet form. Mean AUC and maximum concentrations (C_{max}) were four times greater when posaconazole was administered with a high-fat meal than when it was administered after a fast. Drug exposure was 2.6 times greater when posaconazole was given with a nonfat meal than when it was given after a fast. The authors concluded that posaconazole suspension administered with food is the optimal regimen to ensure maximal systemic exposure.

Ezzet and colleagues conducted a randomized, open-label, crossover study in 18 healthy men to determine the bioavailability of posaconazole when given without food (10). Subjects were given the following doses of posaconazole suspension after fasting for 12 hours: 800 mg once a day (regimen A), 400 mg every 12 hours (regimen B), or 200 mg every 6 hours (regimen C). Subjects continued to fast for 48 hours after the dose was given. The study found that the bioavailability of posaconazole oral suspension increased by 98% when the dose was divided every 12 hours and increased by 220% when the dose was divided every 6 hours in fasting subjects. This was roughly equivalent to posaconazole exposure after a nonfat meal. The authors concluded that divided daily dose administration (either every 12 or 6 hours) increases exposure to posaconazole under fasting conditions.

Sansone-Parsons and colleagues conducted a randomized, open-label, crossover study in 24 adults to determine the effect of a nutritional supplement on the pharmacokinetics of posaconazole (11). Study participants received a single dose of posaconazole 400 mg oral suspension either along with 8 ounces of a nutritional supplement (Boost Plus) or after fasting overnight. The C_{max} and AUC values were higher in subjects who received posaconazole concomitantly with the nutritional supplement. The time to achieve C_{max} and the half-life were not different between groups. The authors concluded that the bioavailability of posaconazole is increased when given with a nutritional supplement.

Based on these studies, it is recommended that posaconazole be administered with food or a nutritional supplement whenever possible (3–5). If a patient cannot be fed, posaconazole should be divided into multiple daily doses (every 6 hours), and the use of alternative antifungal agents should be considered.

Posaconazole has a large volume of distribution, which suggests extensive distribution into the extravascular spaces and penetration of body tissues (3–5). Posaconazole is >95% protein bound, mainly to albumin. The drug undergoes glucuronidation in the liver by the UDP-glucuronosyltransferase 1A4 enzyme to inactive metabolites (3–5, 12). Posaconazole is not metabolized by the cytochrome P450 (CYP450) enzyme system, and studies found no major oxidative metabolites circulating in plasma after posaconazole administration. However, posaconazole was found to inhibit the CYP450 3A4 enzyme (13). Posaconazole is eliminated primarily in the feces as parent compound (66%) (3–5). Less than 1% of the parent compound is eliminated via renal excretion. The elimination half-life of posaconazole is 25 to 35 hours.

In clinical studies, posaconazole pharmacokinetics were not significantly affected by a subject's age, race, or gender (3–5).

A single-dose study in 24 patients evaluated the pharmacokinetic parameters of posaconazole 400 mg given orally with a high-fat breakfast in patients with normal renal function and patients with mild to severe renal dysfunction (14). The four levels of renal function were normal (creatinine clearance [CL_{CR}] >80 mL/min), mild dysfunction (CL_{CR} 50–80 mL/min), moderate dysfunction (CL_{CR} 20–49 mL/min), and severe dysfunction (CL_{CR} <20 mL/min and receiving hemodialysis).

Each patient received one 400-mg dose of posaconazole with a high-fat breakfast. Hemodialysis patients received a 400-mg dose of posaconazole between hemodialysis days and then another 400-mg dose 6 hours before hemodialysis. The second dose was administered after a 3-week washout period. The study found that mild, moderate, or severe renal dysfunction did not significantly alter the pharmacokinetics of posaconazole, and no dosage adjustment is required in these patients. Additionally, posaconazole is not removed by hemodialysis. Liver enzyme levels were elevated in five patients, but four of these patients had elevated levels at baseline as well.

Posaconazole should be used with caution in patients with hepatic dysfunction (3–5). No specific dosage adjustments are recommended due to the lack of definitive pharmacokinetic data.

A multicenter, open-label, parallel-group study was conducted to determine the pharmacokinetic and safety profiles of varying doses of posaconazole in 98 patients with persistent febrile neutropenia or refractory invasive fungal infections (IFIs) (15). Patients received one of three dosage regimens: posaconazole 200 mg four times daily for nine doses followed by 400 mg twice daily (group 1), posaconazole 400 mg four times daily for nine doses followed by 600 mg twice daily (group 2), or posaconazole 800 mg four times daily for five doses followed by 800 mg daily (group 3). Posaconazole was administered with food when possible. The majority of patients (66%) started the study with febrile neutropenia. Patients in group 1 achieved the highest mean exposure ($P = 0.01$). This indicates that doses higher than 800 mg and doses given once daily do not increase drug exposure. Drug exposure in patients who had undergone bone marrow transplantation was 52% lower than in patients who had not undergone transplantation ($P = 0.003$), a result primarily due to an increased elimination rate in transplant patients. However, the number of transplant patients was small (n = 12), and the effect of drug interactions with other medications or severe mucositis was not taken into account in the analysis.

Table 2. Susceptibilities of *Candida* species to various antifungal agents*

Organism	Antifungal	MIC_{90} (mcg/mL)	Percent inhibited at MIC ≤1 mcg/mL
C. albicans	Posaconazole	0.03	99
	Voriconazole	0.015	99
	Itraconazole	0.12	99
	Fluconazole	0.5	97
C. glabrata	Posaconazole	2	80
	Voriconazole	1	92
	Itraconazole	8	70
	Fluconazole	32	1
C. parapsilosis	Posaconazole	0.25	100
	Voriconazole	0.12	99
	Itraconazole	0.25	99
	Fluconazole	4	78
C. tropicalis	Posaconazole	0.25	99
	Voriconazole	0.12	99
	Itraconazole	0.5	98
	Fluconazole	2	66
C. krusei	Posaconazole	1	98
	Voriconazole	0.5	99
	Itraconazole	1	96
	Fluconazole	64	0
C. lusitaniae	Posaconazole	0.12	100
	Voriconazole	0.06	100
	Itraconazole	0.5	100
	Fluconazole	4	86
C. pelliculosa	Posaconazole	2	44
	Voriconazole	0.5	100
	Itraconazole	NR	NR
	Fluconazole	8	0

*From references 17, 18.

MIC indicates minimum inhibitory concentration; MIC_{90}, MIC required to inhibit the growth of 90% of organisms; NR, not reported.

SPECTRUM OF ACTIVITY

Posaconazole has shown in vitro fungistatic and fungicidal activity against *Candida* species (2–5, 16–21). A global surveillance program that compared in vitro activities of posaconazole, voriconazole, and fluconazole against almost 4000 isolates of *Candida* species found that posaconazole and voriconazole were very active against *Candida* isolates (approximately 98% susceptible at a minimum inhibitory concentration [MIC] <1 mcg/mL) (17). Voriconazole appeared to be more potent than posaconazole for *Candida glabrata* and *Candida pelliculosa*. Both posaconazole and voriconazole were more active than fluconazole for all *Candida* isolates. Another study evaluated the in vitro activities of posaconazole, itraconazole, and fluconazole against 3312 isolates (18). This study found that posaconazole exhibited greater potency than itraconazole and fluconazole for all *Candida* isolates tested. *Table 2* summarizes these results. Pfaller and colleagues evaluated the susceptibilities of *C. glabrata* isolates from around the world to seven antifungal agents (16). In North America, caspofungin, flucytosine, and voriconazole all inhibited >90% of *C. glabrata* isolates at an MIC of ≤1 mcg/mL, while posaconazole inhibited 82% of isolates at an MIC of ≤1 mcg/mL.

Posaconazole has also shown in vitro fungistatic and fungicidal activity against *Cryptococcus neoformans* (3–5, 17, 18). The MIC_{90} values for posaconazole range from 0.015 to 1 mcg/mL, with 100% of isolates being susceptible at an MIC of ≤1 mcg/mL. This is similar to the activity of voriconazole and itraconazole, both of which inhibited 100% of *C. neoformans* isolates at an MIC of ≤1 mcg/mL. In contrast, fluconazole inhibits around 15% of *C. neoformans* isolates at concentrations of ≤1 mcg/mL. The echinocandins have no activity against *C. neoformans*.

Posaconazole has shown potent in vitro activity against *Aspergillus* species (3–5, 22, 23). A global surveillance program evaluated the in vitro activity of the triazole antifungals and AmB against *Aspergillus* species and other filamentous fungi. This surveillance program found that both posaconazole and voriconazole inhibited 94% of all *Aspergillus* isolates tested.

Table 3. Susceptibilities of *Aspergillus* species to various antifungal agents*

Organism	Antifungal	MIC_{90} (mcg/mL)	Percent inhibited at MIC ≤1 mcg/mL
A. fumigatus	Posaconazole	0.5	100
	Voriconazole	0.5	99
	Itraconazole	2	77
	Amphotericin B	1	98
	Caspofungin	0.06	99
A. niger	Posaconazole	1	100
	Voriconazole	1	96
	Itraconazole	2	36
	Amphotericin B	1	100
	Caspofungin	0.06	100
A. flavus	Posaconazole	0.5	100
	Voriconazole	1	100
	Itraconazole	1	100
	Amphotericin B	2	62
	Caspofungin	0.06	100
A. terreus	Posaconazole	0.25	100
	Voriconazole	1	100
	Itraconazole	0.5	100
	Amphotericin B	2	37
	Caspofungin	0.06	100
Aspergillus species	Posaconazole	1	94
	Voriconazole	1	94
	Itraconazole	2	72
	Amphotericin B	2	75
	Caspofungin	0.06	98

*From references 22, 23.

MIC indicates minimum inhibitory concentration; MIC_{90}, MIC required to inhibit the growth of 90% of organisms.

Table 4. Susceptibilities of zygomycetes to various antifungal agents*

Organism	Antifungal	MIC_{90} (mcg/mL)	Percent inhibited at MIC ≤1 mcg/mL
Rhizopus species	Posaconazole	1–4	40
	Voriconazole	1–8+	40
	Itraconazole	1–8+	20
	Amphotericin B	0.5–1	100
	Caspofungin	>8	0
Mucor species	Posaconazole	0.5–8+	67
	Voriconazole	1–8+	33
	Itraconazole	2–8+	0
	Amphotericin B	0.5–1	100
	Caspofungin	>8	0

*From references 22–25.

MIC indicates minimum inhibitory concentration; MIC_{90}, MIC required to inhibit the growth of 90% of organisms.

Another study found that posaconazole, voriconazole, and caspofungin inhibited 98%, 95%, and 98% of *Aspergillus* isolates tested, respectively. Posaconazole, voriconazole, and caspofungin are more potent than AmB against *A. fumigatus*. All of the antifungal agents tested were more potent than AmB against *A. terreus*. These results are summarized in *Table 3.*

Posaconazole also has shown in vitro activity against a number of emerging pathogens, such as *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Rhizopus* species, *Mucor* species, phaeohyphomycetes, and other filamentous fungi (3–5, 22, 23). Posaconazole's activity against the zygomycetes is promising. It appears to be more active than voriconazole and fluconazole against zygomycetes, with MIC_{90} values ranging from 0.125 to 8 mcg/mL. AmB remains the most active agent against zygomycetes, with MIC_{90} values ranging from 0.5 to 1 mcg/mL. *Table 4* summarizes the activity of various antifungals against the zygomycetes.

Studies evaluating the in vitro activity of posaconazole against *Fusarium* species and *Scedosporium* species have yielded mixed results (3–5, 22, 23). Posaconazole has MIC_{90} values ranging from 0.25 to >8 against *Fusarium* species.

CLINICAL TRIALS

Prophylaxis

Ullmann and colleagues conducted a randomized, multicenter, double-blind trial to evaluate the efficacy of prophylaxis of IFIs with posaconazole versus fluconazole in 600 patients with graft-versus-host disease after allogeneic hematopoietic stem cell transplantation (3, 26). A total of 301 patients were randomized to receive posaconazole 200 mg suspension orally three times daily, and 291 patients received at least one dose of posaconazole. A total of 299 patients were randomized to receive fluconazole 400 mg orally once daily, and 288 patients received at least one dose of fluconazole. The primary endpoint was the development of proven or probable IFIs, adverse events requiring discontinuation of study drug, or death due to underlying disease or graft-versus-host disease at day 112 (16 weeks postrandomization). Efficacy was also assessed while patients were receiving treatment. The median duration of antifungal treatment was 111 days for posaconazole and 108 days for fluconazole.

At day 112, 16 patients in the posaconazole group and 27 patients in the fluconazole group experienced a proven or probable IFI (P = 0.074). Seven patients in the posaconazole group and 21 patients in the fluconazole group experienced an IFI due to *Aspergillus* species (P = 0.006). Although complications related to IFI were decreased in the posaconazole group compared with the fluconazole group (1% vs 4%, P = 0.41), all-cause mortality rates were similar between the groups (P = 0.847). Adverse events were similar, although it was noted that one patient treated with posaconazole experienced cyclosporine toxicity and died, which was thought to be possibly related to the study treatment. The authors concluded that posaconazole was superior to fluconazole in preventing invasive aspergillosis and was as effective as fluconazole in preventing IFIs overall. However, since this trial was published only in abstract form, statistical methods, power, and detailed results could not be reviewed.

Cornely and colleagues conducted a randomized, multicenter, open-label, noninferiority study to assess the efficacy of

posaconazole versus standard triazole therapy for prophylaxis of IFIs in 602 high-risk, neutropenic patients (3, 27). Patients received posaconazole 200 mg oral suspension three times daily or standard triazole therapy (fluconazole 400 mg orally daily or itraconazole 200 mg oral solution twice daily) continuously or with each chemotherapy cycle. Patients could be changed to the intravenous formulations of the agents if they could not tolerate oral medication. Posaconazole was changed to AmB 0.3 to 0.5 mg/kg daily if intravenous therapy was needed. The study agents were administered until patients were no longer neutropenic or until the occurrence of an IFI, up to 84 days after randomization. The primary endpoint was the occurrence of proven or probable IFI during the treatment phase (randomization until 7 days after last dose of study drug).

Probable or proven IFIs occurred in 2% of posaconazole-treated patients and 8% of fluconazole- or itraconazole-treated patients (P = 0.0009). All-cause mortality rates were lower in the posaconazole group than in the standard triazole therapy group (16% vs 22%, P = 0.048). Mortality due to an IFI was lower in the posaconazole group as well, but the small study was not powered to show a difference in mortality, so it is difficult to assess the significance of these findings. Adverse events were similar between the groups. The authors concluded that posaconazole is superior to fluconazole and itraconazole for the prevention of IFIs. However, once again this trial was published only in abstract form, so detailed information regarding study design and results could not be reviewed.

Treatment of fungal infections

Posaconazole is currently approved only for use as prophylaxis against IFIs in immunocompromised patients. However, numerous studies and case reports have evaluated the efficacy of posaconazole for the treatment of oropharyngeal candidiasis and refractory fungal infections.

Oropharyngeal candidiasis. Vazquez and colleagues conducted a multicenter, randomized trial to evaluate the efficacy of posaconazole versus fluconazole in the treatment of oropharyngeal candidiasis in 350 patients with HIV (28, 29). Patients received either posaconazole or fluconazole 200 mg oral suspension on day one, followed by 100 mg of the same drug orally once daily for 13 days. Patients self-administered the study medication and were instructed on correct administration of the agents. The primary endpoint was the number of subjects that were clinically cured or improved after 14 days of therapy. Secondary endpoints included the durability of cure as well as adverse effects of study treatment. A modified intent-to-treat analysis was performed, which included patients who were randomized, received at least one dose of study drug, and had a positive baseline culture for *Candida* species.

At day 14, 91.7% of patients treated with posaconazole and 92.5% of patients treated with fluconazole were clinically cured or improved (95% confidence interval, –6.61% to 5.04%). Relapse rates were not statistically different between the groups. The incidence of adverse events was also similar between the groups. The authors concluded that posaconazole is not inferior to fluconazole for treatment of oropharyngeal candidiasis.

Zygomycetes. Greenberg and colleagues conducted an open-label, nonrandomized, multicenter, compassionate-use trial to evaluate the efficacy of posaconazole in the treatment of IFIs intolerant of or refractory to other therapy (30). The investigators then reported on the first 24 patients who received posaconazole for treatment of zygomycosis within this study. All patients received posaconazole 800 mg daily (either as 400 mg twice daily or 200 mg four times daily with food). A total of 79% of patients had a complete or partial response to posaconazole therapy. Almost 90% of these patients received posaconazole as monotherapy. Success rates for the various zygomycete species were as follows: 83% for *Rhizopus* species, 83% for *Mucor* species, 50% for *Rhizomucor* species, and 33% for *Cunninghamella* species. Nine patients out of the 24 died during the study period. Two patients died due to persistent zygomycosis after therapy was withdrawn, and two died after approximately a month of posaconazole therapy. The rest died of underlying illnesses or infectious causes other than zygomycosis. The authors concluded that posaconazole is a treatment option for patients with zygomycosis when other therapy has failed or when AmB treatment has caused toxicity.

Van Burik and colleagues retrospectively evaluated the use of posaconazole as salvage therapy for the treatment of zygomycosis in 91 cases (31). Questionnaires were sent to physicians participating in the compassionate-use program sponsored by the manufacturer of posaconazole. Patients were enrolled in this program if they had disease progression or failure while receiving antifungal therapy or if they developed intolerance to antifungal therapy. Posaconazole was given as an 800-mg daily dose divided into two or four doses and given with food. Complete and partial responses were seen in 60% of patients at week 12 of therapy with posaconazole. This result is comparable to previously published success rates with AmB formulations. Treatment failures were seen in 17% of patients who received posaconazole. A total of 38% of patients died while receiving study therapy or within 1 month of follow-up after the drug was discontinued. This case series adds further support to the growing data that posaconazole may be an alternative treatment for zygomycosis when patients are refractory to or intolerant of AmB products.

Aspergillosis. The current standard of care for the treatment of invasive aspergillosis is voriconazole, due to its superiority in clinical trials over AmB (32, 33). Voriconazole is active against *Aspergillus*, including *A. terreus,* which is generally resistant to AmB (34, 35).

Posaconazole has been shown in animal models to have lower MICs than AmB against *A. terreus* (35). A retrospective chart review evaluated 65 patients with IFIs caused by *A. fumigatus* and *A. terreus* (34). Posaconazole, when used as salvage therapy, achieved a response rate of 44% for the treatment of IFIs due to *A. terreus*. Response rates to the various antifungal agents can be reviewed in *Table 5.*

Based on the available clinical data, it appears that posaconazole may be an alternative to voriconazole and AmB for the treatment of IFIs caused by *Aspergillus* species. However, until randomized, controlled clinical data are available, voriconazole

Table 5. Response to antifungal therapy in patients with invasive aspergillosis due to *Aspergillus fumigatus* or *Aspergillus terreus**

Treatment	Mean daily dose	*Aspergillus fumigatus* (n = 33)		*Aspergillus terreus* (n = 32)	
		No. of patients	Patients with responses (%)	No. of patients	Patients with responses (%)
ABLC	5 mg/kg	12	3 (25)	16	3 (19)
LAMB	5 mg/kg	11	4 (36)	11	2 (18)
ABCD	5 mg/kg	2	0 (0)	2	0 (0)
Amphotericin B	1 mg/kg	3	1 (33)	2	0 (0)
Itraconazole	400 mg	5	1 (20)	1	0 (0)
Posaconazole	800 mg	8†	4 (50)	9†	4 (44)

*Reprinted with permission from Hachem et al, 2004 (34).

†Patients experienced failure after receiving a lipid formulation of amphotericin B and were subsequently treated with posaconazole.

ABLC indicates amphotericin B lipid complex; LAMB, liposomal amphotericin B; ABCD, amphotericin B colloidal dispersion.

should continue to be the first-line treatment for invasive aspergillosis.

Other fungal infections

Posaconazole has shown promise in the treatment of invasive fusariosis, *Scedosporium apiospermum* infections, disseminated phaeohyphomycosis due to *Exophiala spinifera*, and refractory coccidioidomycosis infections (36–40). Posaconazole may be considered an option for these infections when patients are refractory to or intolerant of standard antifungal therapy (4, 5).

The safety and efficacy of posaconazole for the treatment of 39 patients who had central nervous system (CNS) infections refractory to or intolerant of other antifungal therapy were evaluated in a small observational study (41). Most patients had underlying HIV infections. The majority of the CNS infections (29 out of 39) were caused by *Cryptococcus* species. The rest of the patients were infected with the following organisms: *Aspergillus* species (four cases), *Pseudallescheria boydii* (two cases), *Coccidioides immitis* (one case), *Histoplasma capsulatum* (one case), *Ramichloridium mackenziei* (one case), and *Apophysomyces elegans* plus a *Basidiomycetes* species (one case). Patients received posaconazole 800 mg daily in two or four divided doses. A total of 14 patients (48%) with cryptococcal CNS infection achieved a successful outcome, defined as complete or partial response to therapy. Five patients (50%) with CNS infections caused by other pathogens achieved a successful outcome. The authors concluded that posaconazole may be an alternative for CNS fungal infections when other antifungal therapy has failed or is not tolerated.

Resistance

The development of fungal isolates resistant to posaconazole has not been adequately reported (4, 5). Posaconazole-resistant *Candida* isolates have been observed while patients were receiving the agent for prophylaxis. These isolates also developed reduced susceptibility to other triazole antifungal agents, suggesting the potential for cross-resistance. However, some studies indicate that fungal infections resistant to older triazole agents may still be successfully treated with posaconazole. Further data are needed to determine the clinical significance of these findings.

ADVERSE EFFECTS/TOXICITIES

Data from clinical trials indicate that posaconazole is well tolerated, even with long-term administration (3–5, 42). The most commonly reported adverse events were fever, diarrhea, nausea, vomiting, and headache. Other notable adverse events included hypokalemia, rash, thrombocytopenia, and abdominal pain.

Elevated liver enzyme levels, hyperbilirubinemia, and hepatocellular damage have been reported with posaconazole therapy (3). The incidence of these adverse events was similar to that with itraconazole and fluconazole. These enzyme elevations were generally mild and resolved upon discontinuation of therapy. Fatalities due to hepatic failure were noted in a small number of patients with serious underlying diseases and were mainly seen in patients receiving treatment doses of posaconazole. Liver function tests should be monitored at baseline and throughout posaconazole therapy, and treatment should be discontinued if serious hepatic abnormalities occur.

Other rare serious adverse events seen with posaconazole therapy include hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, pulmonary embolus, adrenal insufficiency, and allergic and/or hypersensitivity reactions. Prolongation of the QT interval may be seen with posaconazole as well as with the other triazole antifungals. One patient in clinical trials developed torsades de pointes.

DRUG INTERACTIONS

Posaconazole inhibits the CYP3A4 hepatic enzyme and can be expected to increase concentrations of drugs primarily metabolized through this pathway (3, 4, 13). An open-label trial in healthy subjects found that posaconazole increases tacrolimus concentrations twofold (43). Another trial found that cyclosporine concentrations were increased by approximately 30% when administered with posaconazole (44). Serious adverse events, including nephrotoxicity and death, due to increased levels of cyclosporine were noted in clinical trials (3). Frequent monitoring of drug levels and dosage reductions of cyclosporine, tacrolimus, and sirolimus should be instituted when these drugs are administered concomitantly. *Table 6* summarizes these and other drug interactions seen with posaconazole due to the inhibition of CYP3A4.

The effect of an antacid on posaconazole absorption was evaluated in a randomized, open-label, crossover, single-dose trial in 12 healthy adult men under fasting and nonfasting conditions (45). Patients were randomized to the following treatment groups: posaconazole 200 mg after a 10-hour fast, posaconazole 200 mg immediately after a 20-mL dose of an

Table 6. Drug interactions with posaconazole*

Concomitant drug	Interaction	Recommendation
Cyclosporine	↑ cyclosporine concentrations	**Decrease cyclosporine dose by 25%,** monitor levels frequently
Tacrolimus	↑ tacrolimus concentrations	**Decrease tacrolimus dose by 33%,** monitor levels frequently
Sirolimus	↑ sirolimus concentrations	Monitor sirolimus levels frequently, adjust dosage as necessary
Midazolam	↑ midazolam concentrations	Monitor for benzodiazepine adverse effects, adjust dosage as necessary
Terfenadine, astemizole, pimozide, cisapride, quinidine	↑ concentrations of these agents	**Contraindicated** (due to potential for QT prolongation)
Ergot alkaloids	↑ ergot alkaloid concentrations	**Contraindicated** (due to potential for QT prolongation)
Vinca alkaloids (vincristine, vinblastine)	↑ vinca alkaloid concentrations	Consider reduction in dosage of vinca alkaloids to reduce risk of neurotoxicities
HMG-CoA reductase inhibitors (statins) metabolized by CYP3A4	↑ statin concentrations	Consider dose reduction of statins to reduce risk of rhabdomyolysis
Calcium channel blockers metabolized by CYP3A4	↑ concentrations of these agents	Monitor for hypotension, reduce dosage if necessary
Rifabutin	↑ rifabutin concentrations ↓ posaconazole concentrations	Avoid concurrent use unless benefits outweigh risks
Phenytoin	↑ phenytoin concentrations ↓ posaconazole concentrations	Avoid concurrent use unless benefits outweigh risks
Cimetidine	↓ posaconazole concentrations	Avoid concurrent use unless benefits outweigh risks

*From references 3–5.

aluminum and magnesium hydroxide antacid (Mylanta) after a 10-hour fast, posaconazole 200 mg immediately after a 20-mL dose of antacid and following a standard high-fat breakfast, or posaconazole 200 mg after a standard high-fat breakfast. Posaconazole was given in tablet form rather than as suspension. The study found that coadministration of an antacid with posaconazole had no significant effects on its bioavailability under fasting or nonfasting conditions.

Other clinical studies have shown that posaconazole does not affect the metabolism of zidovudine, lamivudine, ritonavir, or indinavir (3). Posaconazole also did not affect the metabolism of glipizide, but some healthy subjects experienced hypoglycemia when the combination was given. It is prudent to monitor blood glucose carefully when posaconazole is administered with glipizide.

DOSE/DOSAGE FORMS

Posaconazole is supplied as a 40-mg/mL oral suspension in 4-ounce amber bottles (3). The dose of posaconazole for prophylaxis of IFIs in immunocompromised patients is 200 mg three times daily (3–5, 26, 27). The dose of posaconazole for the treatment of fungal infections is 800 mg daily given in two or four divided doses (4, 5, 28–31, 36–41). Each dose of posaconazole should be given with a full meal or liquid nutritional supplement to enhance absorption. If a patient cannot tolerate feedings, alternative antifungals should be considered.

PHARMACOECONOMICS

When used for prophylaxis, posaconazole is more expensive than intravenous and oral fluconazole and oral itraconazole. However, due to erratic absorption, itraconazole is not commonly used for prophylaxis against IFIs at Baylor University Medical Center. When used for treatment of fungal infections, posaconazole is less expensive than intravenous voriconazole but more expensive than oral voriconazole. It is also less expensive than caspofungin or lipid formulations of AmB.

It is recommended that posaconazole be considered for use in the treatment of fungal infections caused by zygomycetes. It may also be considered a second-line agent for refractory fungal infections caused by *Aspergillus* species and other filamentous fungi. Additionally, it may be used as prophylaxis against IFIs in patients with hematologic malignancies at a high risk of infection. Posaconazole should not be routinely used for oropharyngeal candidiasis.

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